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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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JAMES H. MEADOWS AND MEDICUS ASSOCIATES
2804 KENTUCKY
JOPLIN, MO 64804

EXAMINER
LUCAS, ZACHARIAH

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 09/25/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/759,112	MULLER ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *16-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group III, and invention A in Paper No. 9 is acknowledged. The Applicant's traversal in on the grounds that the separate inventions within Group II are intended to be used together. The Examiner agrees, and withdraws the restriction. Further, the Examiner also withdraws the restriction between Groups I-III. However, the restriction is maintained between the inventions of Groups I-II, Groups IV-VI, Group VII, and Group VIII.

The requirement is still deemed proper and is therefore made FINAL.

2. The Examiner appreciates the Applicant's corrective remarks regarding the CDR and FR regions in Groups I and II. However, the Examiner would like to clarify that, although claim 12 (referred to as claim 11 in the Applicant's response on page 2) reads on a vector including at least one CDR or FR of the antibody, this claim merely sets forth a minimum requirement for the claimed vector. As such, the claim includes within its scope a vector encoding all of the CDR and FRs of the antibody. Thus, the claim properly belongs in the identified Group as the subject matter included therein is generic to the elected invention.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. The term "substantially identical" in claims 4 and 7 is a relative term which renders the claim indefinite. The term " substantially identical " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. In view of the above, the identified claims are rejected for indefiniteness.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 11, 14, and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims describe a genus of polynucleotides encoding any anti-idiotypic antibody that binds to a human or primate anti-HIV antibody.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical

> and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

In the present application, the Applicant has provided only one example of such an antibody. All of the sequences disclosed by the Applicant are drawn either to either the light or heavy variable regions of the 1F7 antibody, fragments thereof, or promoters used to produce such. Thus, the Applicant has provided only one example of an anti-idiotypic antibody against anti-HIV antibodies. Because one of ordinary skill in the art would not be able to determine from the claims or the specification whether a specific polynucleotide encoding an antibody (or region thereof) other than 1F7 falls within the claimed invention, the Applicant has not provided sufficient written description support for the full scope of the claims.

7. Claims 1-8, 11-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides encoding the sequences of SEQ ID NO: 5 or 24, does not reasonably provide enablement for polynucleotides encoding only the sequence of fragments of the complete variable regions lacking one or more of the CDRs, or encoding variable regions of antibodies other than 1F7 that can bind anti-HIV antibodies. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The claims have been described above, as have the teachings of the application.

The claims are rejected on three grounds. First, the Applicant has not provided an enabling disclosure for any polynucleotide sequence encoding a variable region of any antibody other than the 1F7 antibody. Second, the Applicant is not enabled for polynucleotides that encode either all of the FR and CDR regions of the antibody in an order other than that disclosed in SEQ ID NOs: 7 and 24. Third, the Applicant is not enabled for polynucleotides that encode only FR sequences from the anti-idotypic antibodies.

First, the Applicant is not enabled for polynucleotides that encode the CDRs and FRs of antibodies other 1F7 that bind anti-HIV antibodies because the Applicant has not provided sufficient guidance such that one skilled in the art could make or use such polynucleotides without undue experimentation. As indicated above, the Applicant has provided only one example of an anti-idiotypic antibody that targets anti-HIV antibodies. No other guidance is provided that would lead those in the art to any such other antibodies, or to the polynucleotide sequences encoding them.

Further, the art recognizes that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity that is characteristic of the parent immunoglobulin. It is expected

that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 79: 1979). Rudikoff et al. teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Thus, the art demonstrates that the binding ability of antibodies is highly sequence dependant, and that the effects of a single residue substitution are unpredictable. This, in turn, indicates that the sequences of antibodies targeting any given molecule would likewise be unpredictable.

In view of the broad scope of the claims, the limited examples and teachings in the application, and the complexity and unpredictability of the art, the Applicant is not enabled for polynucleotides encoding any portion of any anti-idiotypic antibodies targeting anti HIV antibodies, other than the 1F7 antibody.

Second, the Applicant has not provided an enabling disclosure for polynucleotides that encode all of the CDRs of the disclosed heavy and light chains where the CDRs are not in the order identified in the disclosed variable chain sequences. As indicated above, the art teaches that a change in the CDRs of an antibody may, unpredictably, alter to specificity of antibody binding. Thus, while the Applicant may be enabled for polynucleotides that encoding individual CDRs for splicing into a humanized antibody, the Applicant has not provided any support for polynucleotides that encode all of the CDRs, but do not maintain them in their proper order. In

view of the unpredictability in the art, and the lack of guidance by the Applicant, the Applicant is not enabled for polynucleotides that encode all of the CDRs in other than the order provided in SEQ ID NO: 7 and 23.

Third, the Applicant is not enabled for polynucleotide encoding only an FR sequence of the 1F7 antibody. While polynucleotides encoding the CDRs, or CDRs with FRs may be used for the creation of humanized antibodies, humanized antibodies are not usually understood to include only the FR sequences of the non-human variable regions. See e.g., Black et al. (U.S. Patent 6,506,383, cols. 6-7 - teaching that humanized antibodies are generally formed by applying the entire non-human variable regions to a human constant region, or by placing the non-human CDRs within human framework sequences), Holmes et al. (J Immunol 167: 296-301, at 301), and Haruyama et al. (Biol Pharm Bull 25(12): 1537-45, at 1537-39, teaching humanization of murine anti-Fas antibody). Because the Applicant has not demonstrated that the FRs are able to bind to human or primate anti-HIV antibodies, and because the Applicant has not demonstrated a use for polynucleotides that encode only the FR sequences of the antibodies, the Applicant is not enabled for the use of these polynucleotides.

8. Claims 4 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides comprising at least one of the claimed CDR sequences, does not reasonably provide enablement for polynucleotides encoding polypeptides substantially identical to those sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. These claims read on any

polynucleotide encoding any polypeptide that is substantially identical to the polypeptides identified in the claims. However, while the sequences of the FRs may be adjusted without a loss in binding specificity, the same is not necessarily true with regards to the CDR sequences.

The Applicant has identified the CDRs and FRs of the 1F7 antibody. However, the Applicant has not demonstrated that any changes may be made to the CDR sequences without a loss of the antibody specificity. No working examples have been provided of polynucleotides encoding such substantially identical CDRs, wherein antibodies comprising such sequences maintain their binding specificity. Nor has the Applicant provided any guidance as to which residues may be susceptible to manipulation.

Further, as indicated above, the art surrounding the specificity of antibody binding sequences is complex and unpredictable. Thus, one skilled in the art would not recognize that the sequences of the CDRs may be manipulated without a loss in binding specificity. Thus, in view of the limited teachings by the Applicant, and the unpredictability in the art, the Applicant is not enabled for polynucleotides encoding polypeptides substantially similar to the identified CDR sequences.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-8, 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Holmes et al., U.S. Patent 5,928,904. These claims read on polynucleotides encoding the CDRs represented by the polypeptides of claim 4, or polynucleotides encoding at least one CDR or FR of the antibody 1F7. The reference discloses an antibody variable heavy chain sharing the first 2 CDRs and the first two FRs of SEQ ID NO: 7 in the present application, and a variable light chain sharing the first two CDRs and the third FR in SEQ ID NO: 24 of the present application. See, Patent, SEQ ID NO: 10, and SEQ ID NO: 2. The reference also discloses a polynucleotide encoding for those chains. See, SEQ ID NO: 3, and SEQ ID NO: 1. The reference also teaches the making of humanized antibodies comprising the CDRs of the sequences, and discloses polynucleotides encoding the CDRs. See e.g., col. 9, lines 3-13, and the sequences identified therein. The reference also discloses a polynucleotide encoding SEQ ID NO: 10 of the patent (SEQ ID NO: 9). This polynucleotide encodes two of the CDRs and two of the FRs of SEQ ID NO: 7 of the present case. It is noted that the present claims specify that the CDRs and FRs be from the 1F7 antibody. However, because the CDRS and FRs of the patent (and the sequences of SEQ ID NO: 3 encoding them) are structurally identical to those of 1F7, the source of the sequences is not deemed sufficient to render the present claims patentably distinct from the art. The reference therefore anticipates the identified claims.

11. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Lohman et al., Gene 105: 283-84). This claim reads on any isolated polynucleotide that contains a sequence encoding at least one CDR or FR of an anti-idiotypic antibody that binds to human or primate anti-HIV antibodies. Lohman teaches polynucleotide sequences encoding the anti-idiotypic antibody MC1.

This antibody is described in Zhou et al. (Virology 174: 9-17) as binding to a chimpanzee anti-HIV antibody. Thus, the reference teaches a polynucleotide that encodes at least 1 CDR or FR as per claim 1.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 12, 14, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Homes et al., (supra) in view of Black et al. supra). The claims read on vectors comprising at least one CDR or FR of the antibody 1F7. As indicated above, Holmes teaches an antibody variable heavy chain sequence sharing the same first two CDRs and FRs with SEQ ID NO: 7 of the present case. The reference also teaches the making of humanized antibodies corresponding thereto. Black et al., teaches methods of humanizing an antibody. From these two references, it would have been obvious to those in the art to make polynucleotides encoding at least one of the CDRs and FRs of the disclosed sequence to make a humanized antibody. In order to produce the humanized antibodies, one of ordinary skill in the art would have to insert the polynucleotides into a vector. Thus, the reference renders the identified claims obvious.

Conclusion

14. No claims are allowed. The subject matter of claims 9 and 10 appears to be free of the art. The claims are objected to as depending on rejected claims.

15. The following prior art references are made of record and are considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

> Kasai et al. (J Immunol Methods 155: 77-89). This reference teaches polynucleotides that encode an anti-idiotypic antibody that binds to an anti-HIV antibody. However, the anti-HIV antibody to which it binds, antibody 0.5β, is a murine antibody. See, Matsushita et al. (J Virol 62: 2107-14).

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner

JAMES HOUSEL 9/22/03
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600